INTERNATIONAL JOURNAL

OF

ADVANCED PHARMACEUTICAL SCIENCES

Volume 1, Issue 01, 117-130 ISSN:2456-8147

GASTRORETENTIVE DRUG DELIVERY SYSTEM A DETAILED REVIEW

Priyanka Mistry[1],S Pani [2]

1,2-Asst Professor, Jeypore College of Pharmacy,Jeypore,Odisha

Article Received on

04.10.17

Revised on

12.10.17

Accepted on

24.10.17

***Corresponding Author**

Priyanka Mistry,

Research Scholar,

Jeypore College of Pharmacy

ABSTRACT

Oral controlled release (CR) dosage forms (DF) are extensively accustomed improve medical aid of the many vital medications. The present study gives a detailed information on The bioavailability of medication with an absorption window in the higher small intestine is usually restricted to pharmaceutical dosage forms. The residence time of such systems and, thus, of their drug unleash into the abdomen and higher bowel is usually short. To beat this restriction and to extend the bioavailability of those medication, controlled drug delivery systems, with a prolonged duration within the abdomen, is used. Incorporation of the drug into a CR-delivery system, that releases its payload within the abdomen over a prolonged fundamental measure, will cause important therapeutic benefits as a result of numerous pharmacokinetic (PK) and pharmacodynamic aspects.

Keywords: **Pharmacodynamics, CR**

Introduction:

Gastroretentive dosage forms (GRDFs) are designed to be maintained within the abdomen for a prolonged time and unleash their active ingredients and thereby modify sustained and prolonged input of the drug to the higher a part of the gastrointestinal (GI) tract[1]. Prolonged stomachic retention improves bioavailability, reduces drug waste and improves solubility for medication that is less soluble in a very high ph environment. it's applications additionally for local drug delivery to the abdomen and proximal small intestines. Gastro retention helps to produce higher accessibility of recent products with new therapeutic possibilities and substantial advantages for patients[3]. This technology has generated monumental attention over the previous couple of decades as a result of its potential application to enhance the oral delivery of some necessary medication that prolonged retention within the higher gi tract can greatly improve their oral bioavailability and/or their therapeutic outcome.

The challenge to develop economical gastro-retentive indefinite quantity forms began close to concerning twenty years past, following the invention of Helicobacter pylori by Warren and Marshall. several attempts are created to plot an extended unleash GRDDS wherever the indefinite quantity kind is little enough to ingest and so preserved within the GI space for a long enough time for the active agent to be dissolved and eventually absorbed[1].

Drugs that are needed to be developed into gastro-retentive dosage forms include:

- Drugs acting locally within the abdomen.
- Drugs that are primarily absorbed within the stomach.
- Drugs those are poorly soluble at alkaline ph.
- Drugs with a relative low window of absorption.
- Drugs quickly absorbed from the gastrointestinal tract and
- Drugs that degrades within the colon[4].

Numerous medication has their greatest therapeutic impact once discharged within the abdomen, notably once the release is prolonged in a very continuous, controlled manner. medication delivered in this manner have a lower level of aspect effects and supply their therapeutic effects

while not the necessity for repeated dosages or with a low dosage frequency. Sustained release within the abdomen is additionally helpful for therapeutic agents that the abdomen doesn't without delay absorb since sustained unleash prolongs the contact time of the agent within the abdomen or within the higher a part of the small intestine, that is wherever absorption happens and call time is restricted. below normal or average conditions, as an example, the material passes through the small} intestine in as little as 1-3 hours. In general, acceptable candidates for CRGRDF ar molecules that have poor colonic absorption but are characterized by higher absorption properties at the higher components of the GIT[1].

The controlled gastric retention of solid dosage forms is also achieved by the mechanisms of mucoadhesion, flotation, deposit, expansion, changed shape systems, or by the simultaneous administration of pharmacologic agents that delay gastric emptying[5].

Gastrointestinal Tract Physiology[5]

Anatomically the abdomen is split into three regions: fundus, body, and antrum (pylorus). The proximal half made of fundus and body acts as a reservoir for undigested material, whereas the antrum is that the main site for mixing motions and act as a pump for gastric removal by propulsive actions. Gastric removal happens throughout fast as well as fed states. The pattern of motility is but distinct within the two states. during the fasting state, an inter-digestive series of electrical events occur, that cycle each through abdomen and intestine each two to three hours.

This is often referred to as the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC), that is additionally divided into following four phases as delineated by Wilson and Washington.

Phase I (basal phase) lasts from thirty to hr with rare contractions.

Phase II (pre burst phase) lasts for forty to hr with intermittent impulse and contractions. because the section progresses the intensity and frequency additionally will increase step by step.

Phase III (burst phase) lasts for ten to twenty minutes. It includes intense and regular contractions for a brief amount. it's because of this wave that each one the undigested material is

sweptback out of the abdomen right down to the small intestine. it's additionally called the housekeeper wave.

Phase IV lasts for zero to five minutes and amount of transition between phase III clinical trial and phase I

Once the intake of a mixed meal, the pattern of contractions changes from fasted to it of fed state. this is often additionally called biological process motility pattern and contains continuous contractions as in the clinical test of the fasted state. These contractions lead to reducing the scale of food particles (to but one mm), that ar propelled toward the pylorus in a very suspension kind. Throughout the fed state onset of MMC is delayed leading to retardation of gastric removal rate.

Factors affecting gastric Retention

Gastric duration of an oral indefinite quantity kind is full of many factors. To withstand the anatomical sphincter into the small intestine the particle size ought to be within the range of one to two millimeter.15 The pH of the abdomen in a fast state is ~1.5 to 2.0 and in the fed state is two.0 to 6.08. The rate of gastric emptying depends in the main on viscosity, volume, and caloric content of meals.The nutritive density of meals helps verify gastric removal time. It doesn't build any distinction whether or not the meal has high protein, fat, or carbohydrate content as long because the caloric content is that the same. However, increase in acidity and caloric price slows down gastric removal time. Biological factors like age, body mass index (BMI), gender, posture, and pathologic states (diabetes, Chron s disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally, females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down[6].

The resting volume of the abdomen is twenty-five to fifty ml. The volume of liquids administered affects the gastric removal time. Once a volume is large, the emptying is quicker. Fluids took at body temperature leave the abdomen quicker than colder or hotter fluids. Studies have discovered that gastric removal of an indefinite quantity kind within the fed state may also

be influenced by its size. Small-size tablets leave the abdomen throughout the biological process section whereas the large-size tablets are empty throughout the housekeeping waves5.

It has been demonstrated using the radiolabeled technique that there's a distinction between gastric removal times of a liquid, digested solid, and nondigestible solid. it had been advised that the removal of large (91 mm) non digestible objects from abdomen was dependent upon inter-digestive migrating myoelectric complicated. Once liquid and digested solids ar gift within the abdomen, it contracts ~3 to four times per minute resulting in the movement of the contents through part opened orifice. Non digestible solids larger than the porta gap are propelled back and several other phases of myoelectric activity occur once the porta gap will increase in size throughout the housework wave and permits the sweeping of the nondigestible solids. Studies have shown that the gastric duration (GRT) is considerably multiplied below the fed conditions since the MMC is delayed[7].

Size and form of dosage unit additionally affect the gastric removal. Garg and Sharma reported that tetrahedron- and rounded devices have an improved gastric residence time as compared with other shapes. The diameter of the dosage unit is additionally equally important as a formulation parameter. dosage forms having a diameter of over seven.5 millimeter show a much better gastric residence time compared with one having 9.9 mm.

The density of a dosage kind also affects the gastric removal rate. A buoyant dosage kind having a density of less than that of the gastric fluids floats. Since it's away from the pyloric sphincter, the dosage unit is maintained within the stomach for a prolonged amount.

Floating units removed from the gastroduodenal junction were shielded from the peristaltic waves during biological process section whereas the nonfloating forms stayed near the pylorus and were subjected to propulsive and retropelling waves of the digestive phase (Figure 1). it had been additionally determined that of the floating and nonfloating units, the floating units were had an extended gastric duration for small and medium units whereas no significant difference was seen between the two types of giant unit dosage forms.

A comparison was created to review the have an effect on of fed and nonfed stages on gastric removal. For this study, all subjects remaining in an upright position got a light breakfast

and another similar group was fed with a succession of meals given at traditional time intervals. it had been ended that as meals got at the time once the previous biological process section had not completed, the floating kind buoyant within the abdomen might retain its position for one more biological process section because it was carried by the peristaltic waves within the higher a part of the stomach[5].

Approaches to design Floating dosage Forms[5,8]

The following approaches are used for the planning of floating indefinite quantity forms of single- and multiple-unit systems.

i) Single-Unit dosage Forms

In Low-density approach4 the globular shells apparently having the lower density than that of gastric fluid is used as a carrier for the drug for its controlled unleash. A buoyant indefinite quantity kind may also be obtained by employing a fluid-filled system that floats within the abdomen.In coated shells, popcorn, price, and polystyrol are exploited as drug carriers. Sugar chemical compound materials like methacrylic chemical compound and cellulose ester phthalate are accustomed undercoat these shells. These ar additional coated with a drug-polymer mixture.

The chemical compound of alternative is either ethyl cellulose or hydroxypropyl polyose looking on the kind of unleash desired. Finally, the product floats on the gastric fluid whereas cathartic the drug gradually over a chronic period. Fluid- filled floating chamber form of indefinite quantity forms includes incorporation of a gas-filled flotation chamber into a microporous element that homes a drug reservoir. Apertures or openings are present on the highest and bottom walls through that the channel fluid enters to dissolve the drug. the other two walls in touch with the fluid are sealed so the unmelted drug remains in this. The fluid present could be air, below partial vacuum or the other appropriate gas, liquid, or solid having an acceptable relative density ANd an inert behavior. The device is of swallowable size, remains afloat at intervals the abdomen for a chronic time, and once the complete release the shell disintegrates, passes off to the intestine, and is eliminated.

Hydrodynamically balanced systems (HBS) are designed to prolong the keep of the dosage form in the gastro internal organ tract and aid in enhancing the absorption. Such systems are best fitted to medication having an improved solubility in acidic setting and additionally for the medication having the specific web site of absorption within the higher a part of the tiny bowel. to stay within the abdomen for a chronic amount of your time the indefinite quantity kind should have a bulk density of but one. It ought to keep within the abdomen, maintain its structural integrity, and unleash drug constantly from the indefinite quantity kind. Various forms of tablets (bilayered and matrix) are shown to own floatable characteristics. Some of the polymers used ar hydroxypropyl polyose, hydroxypropyl methylcellulose, crosspovidone, sodium carboxymethyl cellulose, and ethyl cellulose.

Single-unit formulations are related to issues like projecting along or being closed within the channel, which can have a possible danger of manufacturing irritation.

ii)Multiple-Unit indefinite quantity Forms

The purpose of planning multiple-unit indefinite quantity kind is to develop a reliable kindulation that has all the benefits of a single-unit form and is also empty of any of the higher than mentioned disadvantages of single-unit formulations. In pursuit of this endeavor several multiple-unit floatable indefinite quantity forms are designed.

Microspheres have high loading capability and plenty of polymers are used like simple protein, gelatin, starch, polymethacrylate, polyacrylamide, and polyalkylcyanoacrylate. Spherical chemical compound microsponges, also mentioned as 'microballoons,' are ready. Microspheres have a characteristic internal hollow structure and show a superb in vitro floatability. In Carbon dioxide'generating multiple-unit oral formulations many devices with options that stretch, unfold, or ar inflated by carbon dioxide generated within the devices once administration is delineated within the recent patent literature.

These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 millimeter in their expanded state is exceeded. forms of Gastroretentive indefinite quantity Forms

Expandable systems

The expandable gastro retentive indefinite quantity forms (GRDFs) is intended for the past three decades. They were initially created for numerous veterinary use.By later stage, the planning was changed for an increased drug medical aid in humans. GRDFs ar has basic advantage of easy swallowing and reach the most space of abdomen because of swelling or flowering processes that prolong their gastric retention (GRT). once drug unleashes, their dimensions are decreased with succeeding evacuation from the abdomen. Gastroretentivity is increased by the combination of considerable dimensions with high rigidity of the dosage kind to resist the peristalsis and mechanical contractility of the abdomen. Positive results were obtained in presymptomatic and clinical studies evaluating the GRT of expandable GRDFs.

Bio/Mucoadhesive systems

Bioadhesive drug delivery systems (BDDS) are used as a delivery device at intervals the lumen to enhance drug absorption in a very site-specific manner. This approach involves the employment of bioadhesive polymers, which may adhere to the animal tissue surface within the abdomen. gastric mucoadhesion doesn't tend to be robust enough to impart to indefinite quantity forms the flexibility to resist the robust propulsion forces of the abdomen wall. the continual production of mucose by the gastric tissue layer to exchange the mucose that's lost through peristaltic contractions {and the|and therefore the|and additionally the} dilution of the abdomen content also appear to limit the potential of mucoadhesion as a gastro retentive force.

Some of the foremost promising excipients that are used usually in these systems embrace polycarbophil, carbopol, lectins, chitosan, and gliadin, etc.

Floating drug delivery systems

Floating drug delivery systems (FDDS) have bulk density but gastric fluids and then stay buoyant within the abdomen while not touching gastric removal rate for a chronic amount of your time. whereas the system is floating on the gastric contents, the drug is discharged slowly at the required rate from the system, once unleash of the drug; the residual system is empty from the abdomen.

This leads to AN multiplied GRT and an improved management of the fluctuations in plasma drug concentration. FDDS is divided into non-effervescent and gas-generating system1.

a) Effervescent Systems (Gas-generating Systems):

These buoyant systems used matrices ready with swellable polymers like HPMC, polysaccharides like chitosan, effervescent elements like sodium bicarbonate, acid and hydroxy acid or chambers containing a liquid that gasifies at a vital sign. The best ratio of acid and sodium bicarbonate for gas generation is reported to be 0.76:19.

The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between the two agents. These sublayers were enclosed by a swellable chemical compound membrane containing PVA and purified shellac.

When this technique was immersed within the buffer at 37'C, it settled down and the resolution penetrates into the bubbling layer through the outer swellable membrane. greenhouse gas was generated by the chemical reaction between the two effervescent agents, manufacturing swollen pills (like balloons) with a density but one.0 g/mL. it had been found that the system had sensible floating ability freelance of hydrogen ion concentration and viscosity and therefore the drug (para-amino carboxylic acid) discharged in a very sustained manner28 (Figure two, A and B).

A swellable asymmetric triple-layer pill with floating ability to prolong the gastric duration of triple drug regimen (tetracycline, antiprotozoal drug, and clarithromycin) in Helicobacter pylori. Associated organic process ulcers mistreatment the rate-controlling chemical compound membrane excipients. the planning of the delivery system was supported the swellable uneven triple layer pill approach. 2 medication were incorporated into the core layer of the triple-layer matrix for controlled delivery, whereas the third drug was enclosed in one in all the outer layers for fast unleash. The floatation was accomplished by incorporating a gas-generating layer consisting of metal bicarbonate: carbonate (1:2 ratios) along with the polymers.

b) Non-effervescent Systems:

This type of system, once swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the abdomen. one in all the formulation strategies of such indefinite quantity forms involves the blending of the drug with a gel, that swells in touch with gastric fluid once oral administration and maintains a relative integrity of form and a bulk density of but one at intervals the outer gelatinous barrier. The air unfree by the swollen

chemical compound confers buoyancy to those indefinite quantity forms. Excipients used most ordinarily in these systems embrace hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, PVA, Carbopol, agar, sodium alginate, salt, polythene chemical compound and Polycarbonates1.

The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids (Figure 1.6, A and B)5.

(i) Colloidal gel barrier system

Sheth and Tossounian first designated this hydrodynamically balanced system . Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximises the amount of drug that reaches its absorption sites in the solution form for ready absorption.

This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming chemical compounds like polycarbophil, polyacrylate, and phenylethylene. On coming back in touch with gastric fluid, the matter within the system hydrates and forms a mixture gel barrier around its surface.

(ii) Microporous compartment system

This technology relies on the encapsulation of a drug reservoir within a microporous compartment with pores on its high and bottom walls. The peripheral walls of the drug reservoir compartment ar fully sealed to stop any direct contact of the gastric surface with the undissolved drug. Within the abdomen, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the bowel for absorption.

(iii) Alginate beads

Multi-unit floating indefinite quantity forms are developed from freeze-dried calcium alginate. Spherical beads of roughly two.5 mm in diameter are ready by dropping sodium

alginate resolution into a solution of salt, inflicting the precipitation of atomic number 20 alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40 'C for twenty-four hours, resulting in the formation of a porous system, which may maintain a floating force for over twelve hours. These floating beads gave a chronic duration of over five.5 hours.

(iv) Hollow microspheres / Microballons

Hollow microspheres loaded with a drug in their outer chemical compound shelf were ready by a completely unique emulsion solvent diffusion technique. The ethanol/dichloromethane resolution of the drug ANd AN enteric acrylic chemical compound was poured into an agitated resolution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40'C.

The gas section is generated within the distributed chemical compound drop by the evaporation of chloride fashioned and the internal cavity within the microsphere of the chemical compound with the drug. The micro balloons floated incessantly over the surface of AN acidic dissolution media containing the surface-active agent for over twelve hours.

Mechanism of floating systems[9]

Floating drug delivery systems (FDDS) have a bulk density but gastric fluids and then stay buoyant within the abdomen while not touching the gastric removal rate for a chronic amount of your time. whereas the system is floating on the gastric contents (given within the Figure one.7 (a)), the drug is discharged slowly at the required rate from the system. once unleash of drug, the residual system is empty from the abdomen. This leads to an increased GRT and an improved management of the fluctuations in plasma drug concentration. However, besides a smallest gastric content required to permit the correct action of the buoyancy retention principle, a smallest level of floating force (F) is additionally needed to stay the indefinite quantity kind faithfully buoyant on the surface of the meal. to live the floating force mechanics, a

completely unique equipment for determination of resultant weight has been reported within the literature. The equipment operates by measurement incessantly the force resembling F (as a perform of time) that are needed to take care of the submerged object. the thing floats higher if F is on the upper positive side.

This apparatus helps in optimizing FDDS with relation to stability and sturdiness of floating forces created so as to stop the drawbacks of unpredictable intragastric buoyancy capability variations

F = F buoyanc = (Df - Ds) gv--- (1)

Where, F= total vertical force, Df = fluid density,

Ds = object density, v = volume and

g = acceleration because of gravity.

Applications of floating Drug Delivery Systems:

1. Sustained Drug Delivery

HBS system will stay within the abdomen for long amounts and thus will unleash the drug over a chronic period of your time. the matter of short gastric duration encountered with AN oral controlled unleash formulation, hence, is overcome with these systems. These systems have the bulk density of <1, as a result of that they'll float on the gastric contents.

Recently sustained unleash floating capsules of nicardipine were developed and evaluated in vivo. The formulation compared with commercially out there MICARD capsules mistreatment rabbits. Plasma concentration time curves showed an extended period for administration (16 hours) within the sustained unleash floating capsules as compared with standard MICARD cap (8 hours).

2. Site specific drug delivery:

These systems are notable benefits for medication that ar specifically absorbed from the abdomen or the proximal a part of the tiny bowel eg vitamin B complex diuretic drug and misoprostol. A bilayer floating capsule was developed for native delivery of misoprostol, that

may be an artificial analog of prostaglandin E, used as the protectant of gastric ulcer caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the abdomen, desired therapeutic level might be achieved and drug waste could be reduced.

3. Absorption Enhancement:

Drugs that have poor bioavailability thanks to site specific absorption from the higher a part of the git are potential candidates to be developed as floating drug delivery systems, thereby increasing their absorption. A significant increase in the bioavailability of floating indefinite quantity forms (42.9%) might be achieved as compared with commercially out there water pill (33.4%) and enteric coated LASIX-long product (29.5%).

4. Maintenance of Constant Blood Level:

These systems offer a simple method of maintaining constant blood level with an easy administration and higher patient compliance3.

Limitations of FDDS:

The duration within the abdomen depends upon the biological process state. Hence, FDDS ought to be administered after the meal[10.]The ability to float depends on the association state of the indefinite quantity kind. so as to stay these tablets floating in vivo, intermittent administration of water (a tumbler full, each two hours) is beneficial. The ability of the drug to stay within the abdomen depends upon the topic being positioned upright[11].FDDS don't seem to be appropriate for the medication that has solubility or stability issues within the gastric fluid[12].Drugs like Procardia, that is well absorbed on the complete GIT and that undergoes important initial pass metabolism, might not be fascinating candidates for FDDS since the slow gastric removal might cause the reduced general bio-availability[12].

Conclusion:

GRDDS has immersed as current approach of controlled delivery of the drug that exhibits a system have their own disadvantage. To design a productive GRDDS it's necessary to require into thought the physicochemical events within the git, formulation strategy and proper combination of drug and excipients.

REFERENCES:

[1] Kotta S, Khan AW, Pramod K, Ansari S H, Sharma R K, Ali J (2012) Exploring oral nanoemulsions for bioavailability enhancement of poorly water-soluble drugs. Ex-pert Opin. Drug Deliv. 9(5): 585-598.

[2] Dixit RP, Nagarsenker MS (2008) Self-nanoemulsifying granules of ezetimibe: design,optimization and evaluation. Eur. J. Pharm. Sci. 35: 3183-3192.

[3] Shafiq S, Shakeel F, Talegaonkar S (2007) Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur. J. Pharm. Biopharm. 66: 2227-2243.

[4] Sutradhar K B, Amin M L (2013) Nanoemulsions: increasing possibilities in drug delivery. Eur. J. Nanomed. 5(2): 97–110.

[5] Hamed AC, Vitthal VC, Pravin DC (2013) Self emulsifying drug delivery system: A review. Int. J. Pharm. Chem. Sci. 2(1): 34 – 44.

[6] Chudasama A, Patel V, Nivsarkar M, Vasu K, Shishoo C (2011) A novel lipid-based oral drug delivery system of nevirapine. Int. J. Pharm. Tech. Res. 3(2):1159-1168.

[7] Jingling T, Jin S, Fude C, Zhonggui H (2006) Preparation of self-emulsifying drug delivery systems of *Ginkgo biloba* extracts and *in vitro* dissolution studies. Asian J. Trad.Med. 1: 3-4.

[8] Chime SA, Onyishi VI (2013) Lipid-based drug delivery systems (LDDS): Recent advances and applications of lipids in drug delivery. Afr. J. Pharm. Pharmacol. 7(8):3034-3059.

[9] Reiss H (1975) Entropy-induced dispersion of bulk liquids. J. Colloid Interf. Sci. 53(1):61-70.

[10] Reiss H (1975) Entropy-induced dispersion of bulk liquids. J. Colloid Interf. Sci. 53(1):61-70.

[11] Gajendra S, Khinchi MP, Gupta MK, Dilip A, Adil H, Natasha S (2012) Self emulsifying drug delivery systems (SEEDS): An approach for delivery of poorly water soluble drug. Int. J. Pharm. Life Sci. 3(9): 991-1996.

[12] Constantinides PP (1995) Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharm. Res. 12(11): 1561-72.

[13] Dabros T, Yeung A, Masliyah J, Czarnecki J (1999) Emulsification through Area Contraction. J. Colloid Interf. Sci. 210(1): 222-4.

[14] Wakerly MG, Pouton CW, Meakin BJ, Morton FS (1986) Self-emulsification of vegetable oil-non-ionic surfactant mixtures. ACS Symp Series. 311: 242–55.

[15] Rang MJ, Miller CA (1999) Spontaneous emulsification of oils containing hydrocarbon, nonionic surfactant, and oleyl alcohol. J. Colloid. Interf. Sci. 209(1): 179-92.